A mechanistic insight of phytoestrogens used for Rheumatoid arthritis: An evidence-based review

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ABSTRACT

Assessment of the potential therapeutic benefits offered by naturally occurring phytoestrogens necessitate inspection of their potency and sites of action in impeding the chronic, systemic, autoimmune, joint destructing disorder Rheumatoid arthritis (RA). Possessing structural and functional similarity with human estrogen, phytoestrogen promisingly replaces the use of hormone therapy in eradicating RA symptoms with their anti- inflammatory, anti-oxidative, anti-proliferative, anti-angiogenesis, immunomodulatory, joint protection properties abolishing the harmful side effects of synthetic drugs. Scientific evidences revealed that use of phytoestrogens from different chemical categories including flavonoids, alkaloids, stilbenoids derived from different plant species manifest beneficial effects on RA through various cellular mechanisms including suppression of pro-inflammatory cytokines in particular tumor necrosis factor (TNF-α), interleukin(IL-6) and nuclear factor kappa B (NF-κB) and destructive metalloproteinases, inhibition of oxidative stress, suppressing inflammatory signalling pathways, attenuating osteoclastogenesis ameliorating cartilage degradation and bone erosion. This review summarizes the evidences of different phytoestrogen treatment and their pharmacological mechanisms in both *in vitro* and *in vivo* studies along with discussing clinical evaluations in RA patients showing phytoestrogen as a promising agent for RA therapy. Further investigations and more clinical trials are mandatory to clarify the utility of these plant derived compounds in RA prevention and in managing oestrogen deficient diseases in patients.

1. Introduction

RA is a chronic, inflammatory joint disease which is associated with the production of auto antibodies against immunoglobulin G (IgG) and citrullinated proteins considered as rheumatoid factor (RF) and anti- citrullinated protein antibodies (ACPAs) respectively [1]. This disease mostly affects the flexible (synovial) joints and tissues leading to joint pain, stiffness and swelling mainly caused by hyperplasia of fibroblasts that lined the synovial joints and infiltration of immune cells such as neutrophils, lymphocytes and macrophages [2,3]. Inadequate treatment can lead to permanent cartilage degradation, bone abrasions, joint damage, impaired movement causing irreversible disability [2]. RA is a systemic disease often considered as more than a disease of joints as it simultaneously affects other parts of the body like eyes, lungs, heart and other organs [4]. Nearly 1% of the world gets affected by this disease but its prevalence is found mostly in women [5].

This ubiquity of RA in females more than males with occurrence of 3.6 % in women and 1.7 % in men emphasizes the fact that sex hormones might play a major role in pathogenesis of the disease [6].Among various sex hormones such as estrogen, progesterone and androgens which play role in onset of RA, estrogen deficiency promotes high risk of RA supported by different clinical studies on the use of anti-oestrogen agents [4]. However few studies suggested some inverse role of estrogen in disease progression which makes its role controversial [7]. Several hormonal therapies like hormone replacement therapy (HRT), use of oral contraceptives (OCs) displays protective effects against RA progression [8,9]. Studies reported that this post-menopausal HRT increases spinal bone mineral density (BMD) and maintains femoral BMD in women suffering from RA and helps in preserving bone mass [10] along with reducing inflammation, disease activity score (DAS28) response and radiological joint destruction [11]. In contrary, HRT is often criticized for having some serious negative side effects like weight gain, depression, pelvic pain, irregular bleeding and fear of having cancer [12]. Moreover the commonly used synthetic drugs including the

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Table 1
Phytoestrogens with their plant sources and target diseases.

Phytoestrogen	Plant source	Disease	Reference
		Cancer	[143]
Arctigenin	Onion leaves, semambu leaves, bird chili, black tea, papaya shoots, guava, flowers of *Arctiumlappa*	Alzheimer's disease	[146, 147]

		Clotting	[148]
		Heart diseases	[148]
		Chronic inflammatory cell infiltration	[148]
		Diabetes	[149]
		Cancer	[150]
Bavachin	*P. corylifolia*L.	Antibacterial	[151]
		Anti-inflammatory activities	[152]
		Parkinson's disease	[153]
		Anti-inflammatory	[154]
Biochanin A	Red clover, soy food, alfaalfa	Airway hyper responsiveness	[155]
		Influenza	[156]
		Menopause	[157]
		Androgen mediated diseases	[158] [159]
		Rice blast disease	[160]
Equol	Soybeans	Colitis	[161]
		Bone loss	[162]
		Neural diseases	[163]
		Prostate growth	[164]
		Allergic reactions	[165]
		Alzheimer's disease	[166]
		Viral disease	[167]
Formononetin	*A. membranaceus* extract	Type 2 diabetes	[168]
		Mycorrhizal colonization, Fusarium crown and Root rot	[169]
		Antioxidant	[170]
		Colitis	[161]
		Parkinson's disease	[171]
		Bone resorption	[172]
Genistein	Soy beans and soy protein	Diabetes	[173]
		Lysosomal storage	[174]
		Alzheimer's disease	[175]
		Colitis	[161]
		Cardio-cerebrovascular disease	[176]
		Alzheimer's disease	[177]
Daidzein	Soyabean	Coronary heart disease	[178]
		Cancer	[179]
		Bone metabolism	[180]
		Parkinson's disease	[180]
Hesperidin	Citrus fruits	Alzheimer's disease	[181]
		Cardiac diseases	[182]
	Watercress, mustard green, arugula, spinachkale, endive, radish seeds, dock, turnip greens, garden cress, blueberry, gooseberry, watermelon, kiwi, strawberry, apricot, elderberry, blackberry, peach, cherry	Rheumatoid arthritis	[77]
Kaempferol		Parkinson's disease	[183]
		Alzheimer's disease	[184]
		Breast cancer	[185]
	Celery, parsley, broccoli, onion leaves, carrots, pepper, cabbage, apple skins, chrysanthemum flowers	Alzheimer's disease	[186]
Luteolin		Diabetes	[187]
		Anti-inflammatory	[187]
		Sexually transmitted disease	[188]
Leonurine hydrochloride	Motherwort (*Leonurus cardiac*)	Lung cancer	[189]
		Prevents bone loss	[81]
		3 leaf spot diseases of alfalfa	[190]
		Leukaemia	[191]
Medicarpin	Alfa alfa	Formation of brown and beige	[192]
		Bone loss	[94]
Coumestrol	Soybeans, alfaalfa, clover, sunflower seeds, spinach, legumes	Breast cancer	[193]
		Bone disease	[194]
		Alzheimer's disease	[195]
Puerarin	*Puerariamirifica* extract	Parkinson's disease	[196]
		Coronary heart disease	[197]
		Alzheimer's disease	[198]
		Parkinson's disease	[199]
Resveratrol	Grapes	Non-alcoholic fatty liver disease	[200]

		Cardiac diseases	[201]
		Cardiovascular diseases	[202]
Pinosylvin	Grapevine	Adjuvant arthritis Necrosis in bovine aortic endothelial cells	[108] [203]
Apigenin	*Hypericumperforatum*	AlzheimerAntiviral effects ’s disease	[[144145]]

(*continued on next page*)

Table 1 (*continued*)

Phytoestrogen	Plant source	Disease	Reference
		Allergic reactions	[204]
		Adjuvant arthritis	[108]
		Alzheimer’s disease	[205]
		Cancer	[206]
Pterostilbene	Grapevine	Obesity	[207]
		Type 2 diabetes	[208]
		Pancreatic cancer	[209]
		Alzheimer’s disease	[210]
		Inflammatory bowel disease	[211]
Quercetin	Capers, onions, peppers, tomatoes, shallots, cherries, asparagus, red apples and grapes, broccoli, kale, berries, tea, letuce	Chronic obstructive pulmonary disease	[212]
		Parkinson’s disease	[213]
		Huntington’s disease	[214]
Silibinin	*Silybummarianum*(milk thistle)	Liver disease	[215]
		Hepatitis B or C	[216]
Ginsenoside	*Panax* (ginseng)	Decreases nature of endometriosis	[217]

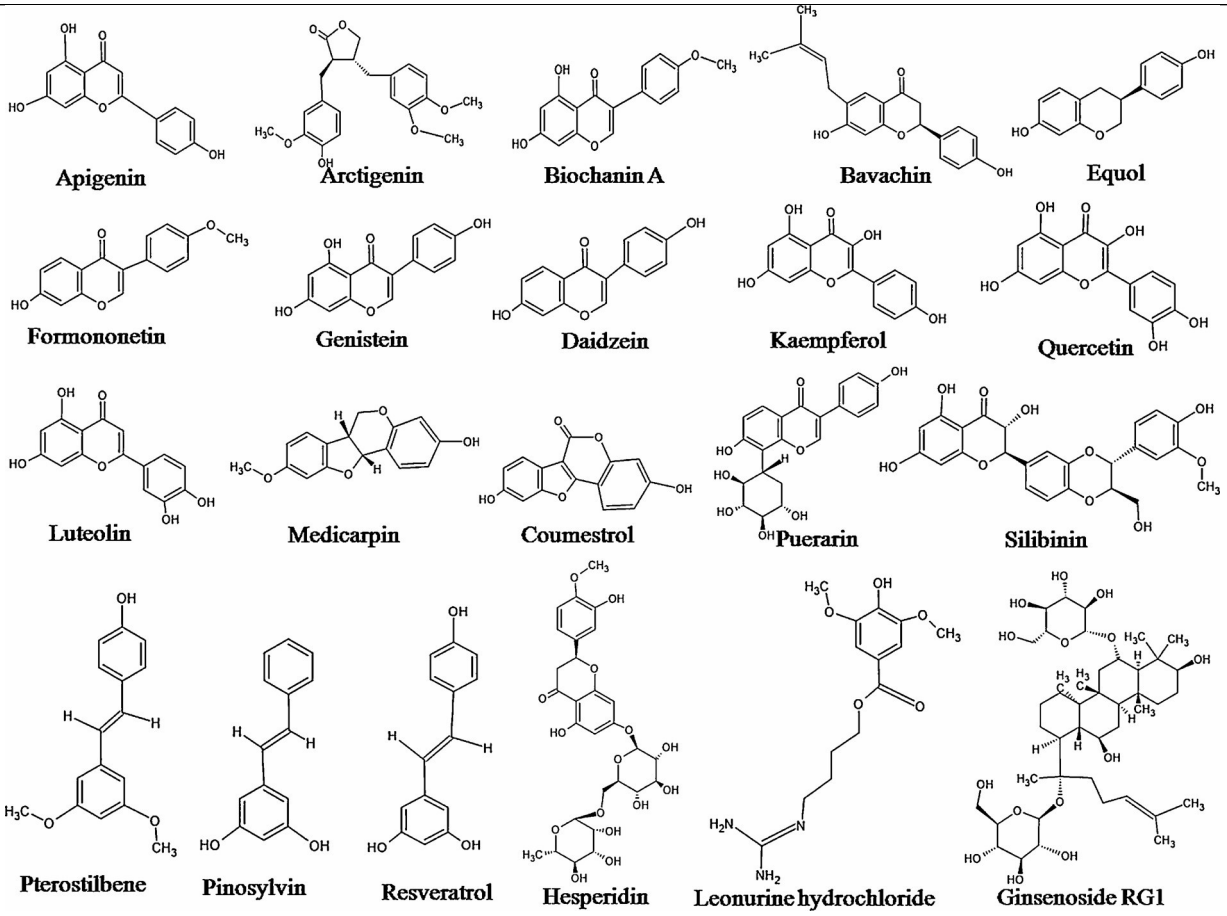

Fig. 1. Structures of phytoestrogens used for preventing Rheumatoid arthritis.

Disease-modifying anti-rheumatic drugs (DMARDs) practised for treating RA are not accurately beneficial to all RA patients and also known to manifest various side effects with significant toxicity [13]. In certain cases combination of HRT and DMARDs reported to be effective in early RA patients [14] but with continuous synthetic therapy patients suffer from

frequent adverse effects and high health care costs [15]. These complications in the usage of synthetic therapies with their limited success for treating RA essentially appeared to raise a demand of phytomedicines with remarkable benefits and barely any side effects. Recently cotherapies of synthetic medicines with phytomedicines is on recent trend and in several studies these combinations proved to be beneficial with minimal side effects [16]. In conclusion phytoestrogen can also be applied in combination with currently used synthetic drugs like DMARDs to implement better efficacy in treating RA and can also minimize the harmful effects of synthetic medicines.

There is an increasing concern of using plant derived estrogen known as the phytoestrogens in replacement of traditional Estrogen Replacement Therapy (ERT) for treating various diseases such as bone disorders, breast cancer, heart diseases, hot flashes or menopausal symptoms and also autoimmune diseases like RA. As 30–40 % women who ever start ERT, refuses to continue it after some time, usage of phytoestrogens as medication are in a recent trend. [17]. Phytoestrogens with their utilization in different diseases are mentioned in Table 1.

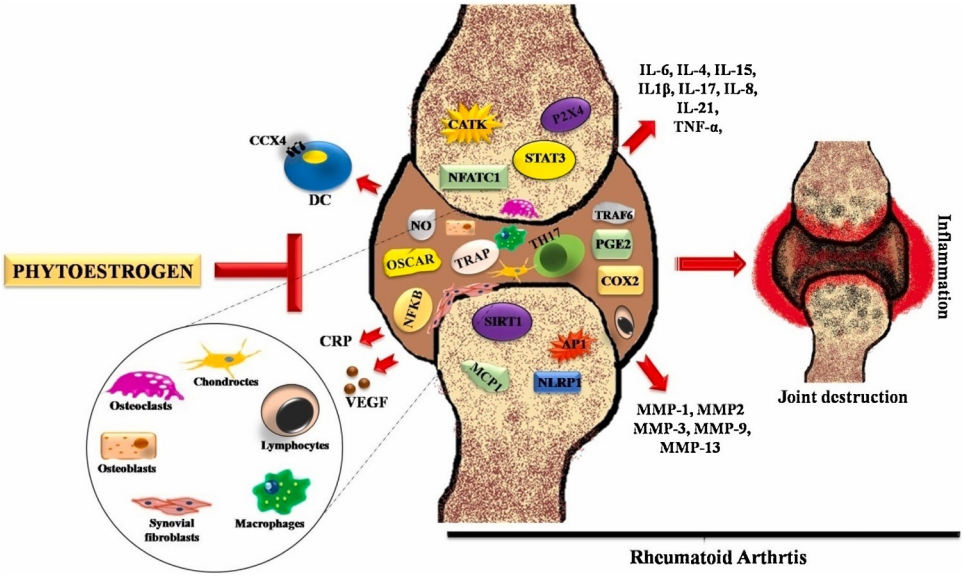

Fig. 2. Phytoestrogens inhibiting cytokines, inflammatory and other disease progressing proteins in RA.

Phytoestrogens are plant derived naturally occurring compounds that act as human estrogen and has the ability to bind to estrogen receptors (ERs) in human in account of possessing chemical structure quite similar to estrogen [18]. Because of having a phenolic ring, phytoestrogens have the capability to bind to both, ERα and ERβ and is present in much higher quantity than endogenous estrogen in the body [19]. The structures of the selected phytoestrogens are demonstrated in Fig. 1. There are three main categories of phytoestrogens; isoflavones, coumestans and lignans and is known to exist in legumes, flaxseed, lentils, whole grains, various fruits and vegetables [20]. Metabolism of phytoestrogens vary from person to person and its dietary intake is known to exhibit anti-inflammatory, anti-carcinogenic, anti-oxidative and other medicinal properties [21,17].

Phytoestrogens exhibits protective nature against various bone disorders, osteoporosis and also arthritis. It is also effective against autoimmune diseases like RA targeting different inflammatory and signalling pathways attenuating the production of cytokines, reducing oxidative stress and preventing osteoclastogenesis [17].

Several *in vitro* cell culture studies, *in vivo* animal experiments and clinical studies had been conducted to certify the potency of phytoestrogens in obstructing the progression of RA in recent years. RA is a systemic disorder and due to chronic inflammation and synthetic medications, patients often experience comorbid conditions such as cardiovascular disease, the most cause of death in RA patients [22]. Efficiency of different phytoestrogens is enquired in various studies for minimising these critical conditions. This review summarizes all these available published data about the medicinal implications of different phytoestrogens and its propitious effects in regulating the pathogenesis of RA to authenticate the use of phytoestrogens as an alternative therapy for RA.

2. Apigenin

Apigenin(AP), chemically known as a 4′, 5, 7,-trihydroxyflavone, with molecular formula $C_{15}H_{10}O_5$ and molecular weight (MW) 270.24 g/mol is a naturally occurring plant flavonoid. It is commonly present in fruits like oranges, grapefruit, vegetables such as parsley, onions, chamomile, wheat sprouts and also in some seasonal vegetables and phytobeverages like tea. Naturally it is found as dimer in the form of biapigenin and is isolated mainly from the buds and flowers of *Hypericum perforatum.* It is also present in red wine and beer and is found in nature mostly in the form of AP-7-*O*-glucoside and various acylated derivatives. It is known to exhibit anti-inflammatory, antioxidant, anticancer and anti-proliferative properties [23]. This flavonoid also played an important role in treating RA in various *in vitro* and *in vivo* experiments.

In 2009, Shin et al. reported the effect of AP in human rheumatoid arthritis fibroblast-like synoviocytes (RA-FLSs) which demonstrated apoptotic cell death and decrease in survival rate mediated through caspase-3 and caspase-7 activation after AP induction in RA-FLSs. Reduction of oxidative stress by production of intracellular reactive oxygen species (ROS) after AP treatment followed by activation of the mitogen-activated protein kinase (MAPK) and extracellular signal- regulated kinase (ERK1/2) were also shown in this study [24]. Another study revealed the pro-apoptotic action of AP as it enhanced the cytotoxic effect of TNF-related apoptosis-inducing ligand (TRAIL) on activated RA-FLSs. TRAIL is known for its pleiotropic effect by inducing apoptosis in a subunit of RA-FLS and also promotes expansion of the surviving cells. [25]. Treatment of AP along with TRAIL increased expression and activity of caspase 3 and decreased B-cell lymphoma (Bcl-2)/Bcl-2 associated x protein (Bax) ratio in comparison to treatment with TRAIL alone. AP also restored the expression of two cell-cycle inhibitors p21 and p27 and inactivatedphosphatidylinositol-3-kinase (PI3- K)/protein kinase B (Akt) signalling pathway which restrained TRAIL induced RA-FLS proliferation sensibilizing RA-FLS to TRAIL-induced apoptosis [26]. *In vivo* study on arthritic rats stimulated by Freund's complete adjuvant (FCA) reported the anti-arthritic property of AP as its induction in arthritic rat model inhibited the expressions of P2 × 7/NF-kB signal-related proteins and inflammatory cytokines like TNF-α, IL-1β and IL-6 [27]. Apigenin showed anti-arthritic effect by modulation of dendritic cell functions which was demonstrated in*in vitro* experiment on Bone marrow-derived dendritic cells (BMDCs) stimulated with lipopolysaccharide (LPS) and also in *in vivo* experiment on collagen-induced arthritis (CIA) rats. Both *in vivo* and *in vitro* experiments showed a reduction in expression levels of co-stimulatory molecules and major histocompatibility complex II (MHC II) on dendritic cells (DCs) and strongly diminished the number of Langerhans cells, but did not affect plasmacytoid DCs (pDCs) in lymph nodes (LNs). This reduction might be associated with the diminishing effect of AP on the expression of chemokine receptor 4 (CXCR4) on DCs leading to inhibition of maturation and migration of DCs contributing to immunosuppressive effects [28]. In 2019, Li et al. demonstrated in CIA model that AP protective effects on arthritis might be *via* inhibition of synovial hyperplasia as increase in apoptosis and decline in fibroblast-like synoviocytes (FLS) proliferation along with repression of CIA angiogenesis were observed in AP treated CIA rats. This repression was mediated through reduction of vascular endothelial growth factor (VEGF) and its receptor (VEGFR) levels. Moreover AP also found to regulate osteoclastogenesis-associated receptor activator of NF-kB ligand (RANKL)/RANK/osteoprotegerin (OPG) system in CIA mice [29]. These studies suggested AP as a potential phytoestrogen that could be utilized in RA therapy due to its anti-proliferative and immunosuppressive properties targeting various signalling pathways responsible for progression of the disease. Demonstration of pathophysiological mechanisms of phytoestrogens in RA is represented in Figs. 2 and 3.

3. Arctigenin

Arctigenin is a natural dibenzylbutylrolactone type lignanolide [30, 31] with chemical formula $C_{21}H_{24}O_6$ and MW372.4 g/mol. Arctigenin is an inhibitor of human deficiency virus type-I integrase [31]. It is a bioactive component isolated from dried seeds of Arctium lappa L. (Compositae) and is used widely as a Traditional Chinese medicine [32]. Due its anti-inflammatory activities, this compound has also been examined in various experiments to identify its potency in protecting RA progression.

Arctigenin had been found to inhibit osteoclast differentiation in bone marrow macrophages and bone resorption which were mediated by RANKL and also suppressed the phosphorylation of ERK1/2 in a study by Kim et al. in 2012. Moreover it significantly suppressed nuclear factor of activated T cells cytoplasmic 1 (NFATc1), c-Fos, TNF receptor associated factor (TRAF6), cellular proto-oncogene tyrosine-protein kinase (c-Src), cathepsin K expression levels, spleen associated tyrosine kinase (Syk), phospholipase (PLCγ2) and growth factor receptor-bound protein 2 associated binding protein (Gab2). This study also reported the prevention of osteoclast differentiation in calvarial bone in LPS-stimulated mice which substantiated the fact that arctigenin can be utilized in preparation of RA and osteoporosis drugs [33]. In RA-FLS, arctigenin played its role

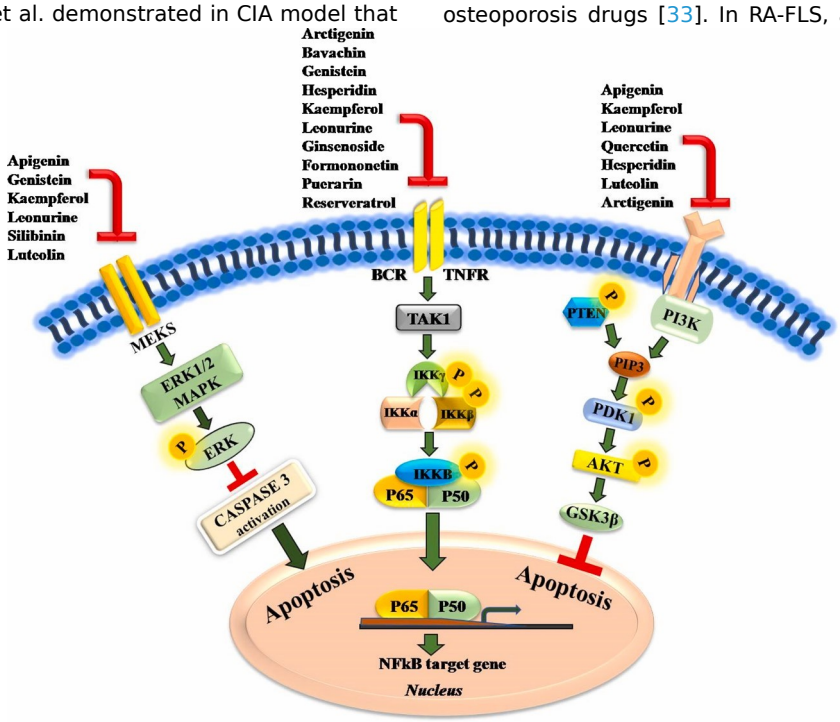

Fig. 3. Pathophysiological mechanism of RA progression and respective phytoestrogens targeting MAPK/ERK1/2 pathway, NFKB pathway and PI3K pathway attenuating progression of RA. MEKS, MAPK/ERK kinase; BCR, B cell receptor; Tumor necrosis factor receptor; TAK, TGF β-activated kinase; PTEN, Phosphatase and tensin homolog; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; PDK1, Protein 3-phosphoinositide-dependent protein kinase-1; GSK3, Glycogen synthase kinase-3.

by inducing apoptosis and decreasing cell viability by 23, 30, and 38 % at a dose of 10, 20, and 30 mM, respectively with38mM as the half maximal inhibitory concentration (IC50). It occurred by decrease of anti-apoptotic protein, Bcl-2 and increase of pro-apoptotic protein, Bax along with mitochondrial membrane potential loss and release of cytochrome C into cytoplasm. Arctigenin also induced mitochondrial apoptosis of RA-FLSs by activating of mitochondrial pathway which leaded to caspase-9, caspase-3, and poly ADP-ribose polymerase (PARP) cleavage. Moreover arctigenin was found to be associated with action of NF-kB and Akt signaling pathways by inhibiting the nuclear translocation of p65, decreasing the degradation of inhibitor of kappa B alpha (IkBa), and attenuating the phosphorylation of Akt [34]. Excessive osteoclast formation which leads to several diseases like RA can be inhibited by arctigenin treatment which was demonstrated *in vivo* on titanium (Ti) particle–induced osteolysis where significant suppression of Ti particle–induced osteolysis and prevention of bone destruction were observed along with inhibition of RANKL-induced osteoclastogenesis, osteoclastic marker genes expression, suppression of receptor activator of NF-κB ligand–induced activation and hydroxyapatite resorption activity. These activities caused the retardation of IκBα degradation and inhibition of p65 nuclear translocation [35]. *In vitro* study on arctigenin treatment in Raw264.7 cells showed the inhibition of TNF-α production which was occurred by repression of mitogen-activated protein kinase kinase (MAPK) activities leading to inhibition of activation of MAPK including ERK1/2, p38 kinase followed by activation protein (AP-1) inactivation [36]. These osteoclast inhibition and attenuation of various disease progressing signalling molecules recommend arctigenin as a vital compound which could be used in RA therapy.

4. Biochanin A

Biochanin A also known as olmelin or pratensolisis an isoflavone with molecular formula $C_{16}H_{12}O_5$ and MW 284.26 g/mol [37]. This bioactive component is present in *Trifolium pratense* (red clover) and many other legumes and is known to target different stages of cell cycle, signal transduction pathways linked with cell differentiation and proliferation, apoptosis and display anti-carcinogenic properties especially in human breast carcinoma. It is also known for targeting, NF-κB, and peroxisome proliferator-activated receptor gamma (PPARγ) and suppresses the activation of Akt and MAPKs causing increase in ERs expression levels [37,38]. Not much is known about this phytoestrogen in targeting RA directly, but related studies were performed to suspect its potential in this case.

In 2016, Oh et al. showed the anti-inflammatory property of Biochanin A in primary rat chondrocytes by reporting the downregulation of matrix degrading enzymes such as matrix metalloproteinase MMP-13, MMP-3, MMP-1, disintegrin and metalloproteinase ADAMTS-5 expression along with IL-1b-induced catabolic factors like nitric oxide synthase 2 (NOS-2), cyclooxygenase-2, prostaglandin E2 (PGE2) and inflammatory cytokines after administration of Biochanin A. In this study it was shown that Biochanin A targeted NFkB signaling by suppressing IL-1b- induced phosphorylation of NFkB and its nuclear translocation and also prevented IL-1b-induced loss of proteoglycans [39]. Study by Qiu et al. in 2011 proved that Biochanin A ameliorated cytokine production by PPARγ dependent pathway in LPS-stimulated mouse RAW264.7 macrophages and also suppression of the secretion of TNFα and IL-6 were observed upon Biochanin A treatment which was supported by the use of antagonist GW9662, antagonist of PPARγ [40]. Reports on Biochanin A revealing its capability in targeting various signalling pathways and down regulating inflammatory proteins propose this compound to be investigated in RA conditions.

5. Bavachin

Bavachin, is a phytoestrogen with molecular formula $C_{20}H_{20}O_4$and MW 324.4 g/mol. Bavachin is included in the group of flavonoids and is found in *Psoralea coryfolia*. It exhibits anti-diarrheal properties and is used as a tonifying drug to tonify renal function, decrease pigmentation by melanin in the skin and also helps in fracture healing, and potentially protect cartilage from inflammation [41]. Several studies were reported of Bavachin treatment in inflammation induced cells which resulted in beneficial outcomes.

Bavachin can be utilized for preventing osteoclast-mediated bone destructive disorders as in a study by Kim et al. it was demonstrated that osteoclatogenesis was inhibited by bavachin treatment in a dose- dependent manner in RAW264.7 cells treated with RANKL along with the decrease of osteoclastogenesis and inflammation associated factors such as Tartrate-resistant acid phosphatase, MMP-9, and cathepsin K, NO, inducible NOS, cyclooxygenase-2, and Pg E2. It was also found to suppress RANKL-induced phosphorylation of NF-κB and successively restrained the translocation of NF-κB from the cytosol to the nucleus [42]. Anti-inflammatory role of bavachin was also being reported in a study where bavachin reduced IL-1β-induced NF-κB but not AP-1 DNA-binding activity and also suppressed NF-κ light polypeptide gene enhancer in B-cells inhibitor. It was also found to subdue alpha IκBα degradation, escalated nuclear translocation of p65 and p50 as well as decreased IκBα kinase (IKK) activity along with inhibition of IL-1β-induced chemokine production that culminated in reduced migration of Tamm-Horsfall protein-1 (THP-1) monocytic cells [43]. These *in vitro* experiments on bavachin assessed this phytoestrogen to be a potential compound for phytotherapy in inflammatory diseases and further specific *in vivo* and clinical studies are needed to use it commercially as phytomedicine for RA.

6. Equol

Equol, chemically known as 4′,7-isoflavandiol, is an isoflavan with molecular formula $C_{15}H_{14}O_3$ and MW242.27 g/mol. It is generally produced by intestinal bacteria and is considered as a metabolite of the soy isoflavones, referred to as nonsteroidal estrogens [44]. Equol possesses strong anti-oxidant, anti-estrogenic, anti-cancerous and anti-inflammatory properties [45].

Anti-inflammatory property of equol was determined in the study by Lin et al. 2016 where CIA mice were administered with equol and an increase in BMD was observed in comparison to control CIA mice and there was a decrease in severity of the symptoms of arthritis. Moreover reduction in IL-6 and its receptor expression were observed along with the suppression of genes linked with attenuation of bone formation, osteoclast and immature osteoblast specificity, and also cartilage damage indicating that equol can play an important role in regulating inflammation and bone metabolism in RA [46]. Another *in vivo* study had also shown that loss of bone and fat aggregation in estrogen-deficient osteoporotic mice was inhibited by equol [47]. These *in vivo* experiments on RA animal models provide a strong indication of equol in delivering protective activities against RA.

7. Formononetin

Formononetin (FMN) is an O-methylated isoflavone with molecular formula $C_{16}H_{12}O_4$ and MW 268.268 g/mol. It is commonly present in legumes, many species of clovers especially red clovers Trifolium pratense L., in traditional Chinese herb Astragalus membranaceus (Fisch) and also in various plants like *Astragalus propinquus Schischkin* and *Spatholobussuberectus* [48,49]. It has a similar structure like endogenous oestrogen (estradiol),which binds to ERs α and β [49]. Formononetin exhibit anti-tumor, anti-bacterial, anti-lipid peroxidation, and estrogen-like activities [48]. This phytoestrogen is well known for its therapeutic activities against RA in both *in vitro* and *in vivo* experiments.

FMN is reported to be an effective therapeutic agent in CIA induced arthritic mice as a dose of 100 mg/kg FMN administered3 times a week for 4 weeks, drastically decreased the arthritis index and there was an inhibition of inflammatory cell infiltration and IκB-α degradation along with controlling the release and expression of NF-κB p65 which hindered cartilage and synovium destruction [48]. FMN was also reported as a responsible component in healing fractures as in a study by Huh et al. in 2009 it was demonstrated that FMN significantly increased the number of vessels and also the expression levels of VEGF and VEGFR-2/flk-1 in a rat fracture model after orally administering FMN at a dose of 20 μg/kg or 200 μg/kg once a day during the healing period of 21 days compared to control rats. Though there was no such difference in effect of FMN in two different doses but marked induction in differentiation of mesenchymal stem cells in the fracture site was noticed after 7 days of administration and after 14 days there was a stimulation of mesenchymal progenitors such as alkaline phosphatase (ALP), osteocalcin (OCN), osteopontin (OPN) and collagen type I (Col I). This signified FMN potential in osteogenic differentiation and fracture healing [50]. Immunomodulatory properties of FMN was also shown in 2016, where FMN was found to decrease Pro-osteoclastogenic subset T-helper 17 (1h-17) and B cells, TH17 differentiation factors, IL-17A-induced osteoclastgenesis along with promoting forkhead box P3 (FOXP3) expression and significant restoration of ovariectomy (Ovx)-induced deterioration of trabecular microarchitecture [51]. These assessments of FMN therapeutic properties against RA manifest its utility as a potential phytocompound for treating RA. Further clinical studies are needed for its certification.

8. Genistein Genistein (Gen) designated as angiogenesis inhibitor falls under the category of soy derived isoflavones with molecular formula $C_{15}H_{10}O_5$ and MW 270.24 g/mol. It is mainly found in soybeans and other legumes like chickpeas [52]. This phytoestrogen is known for its health benefits contributing antioxidant, anti-cancer, anti-neoplastic activity and immunosuppressive activities [53]. Gen is considered as the one of the most common phytoestrogen which exhibits preventive activities against RA pathogenesis supported by various scientific assessments.

Gen is known to exhibit anti-angiogenetic activity and angiogenesis is an important part in RA progression. In 2020,Cheng et al. studied the effect of Gen and reported the inhibition of IL-6 and VEGF expression level and their secretion in MH7A cells along with repressing the nucleus translocation of Signal transducer and activator of transcription 3 (STAT3). Gen has also been found to inhibit the migration and tube formation of vascular endothelial cells induced by IL-6 rendering anti- angiogenic role in human umbilical vein endothelial cells (EA.hy926 cells) [54]. Anti-inflammatory role of Gen which can play role in suppressing RA progression was shown in the study by Li et al. in 2014 where a significant decrease in IL-1β, IL-6, IL-8 expression, prevention of TNF-α-induced NF-κB translocation, phosphorylation of IκB kinase-α/β and IκBα as well as suppression of TNFα-induced AMP activated protein kinase (AMPK) inhibition were observed in TNF-α-stimulated MH7A cells treated with Gen in a dose dependent manner. This study proved that Gen delivers its anti-inflammatory property by activation of AMPK and inhibition of ROS/Akt/NF-κB pathway [55]. Effect of Gen was studied on CIA in mice and a significant inhibition of Delayed type hypersensitivity reaction reaction (DTH) to oxazolone and decrease in granulocyte-mediated response was observed along with reduction in levels of oxazolone-specific antibodies and serum levels of auto antibodies to col II leading to depletion of inflammation and joint destruction [56]. Another study on CIA induced mice by Wang wt al. in 2008 reported that upon Gen treatment there was a significant reduction in interferon (IFN) secretion and production of IL-4 and Gen plays an important role in regulating the Th1/Th2 balance [57]. Gen showed inhibitory role on cell number and 3H thymidine (3 H-TdR) incorporation of RA-FLS stimulated with IL-1β, TNF-α and epidermal growth factor (EGF) and also arrested the cell cycle at G1 restriction point. Moreover Gen inhibited the expression of MMP9 and proliferation of RA-FLS mediated by ERK1/2 [58].In another model of RA, where female Sprague-Dawley rats were induced with col II plus adjuvant, protective effects of Gen was observed as it was found to reduce disease symptoms as well as onset of the disease [59] and also restored paraoxonase and arylesterase activity and diminished malondialdehyde (MDA) concentrations [60]. Paraxonase is found in lower level in RA patients and its reduction leads to serious problem like artherosclerosis which cause comorbid deaths. Thus restoration of paraoxonase by Gen can diminish cardiovascular risk in RA [61]. Gen plays an important role in reducing osteoclast formation as it was demonstrated that Gen at a dose of 10^{-7}M significantly decreased TRAP positive osteoclast formation and resorption area and inhibited the action of estrogen inhibitor ICI 182,780 in causing pro-osteoclastic effect. It also reduced TNF-α-induced *c-fos* and *NFATc1* expression in an estrogen dependent manner along with inhibition of NFATc1 nuclear translocation and *NFκB* and *DC-STAMP* levels in RAW 264.7 cells [62]. In 2020, Du et al. revealed the ability of Gen in protecting bone and joint damage in CIA model of female DBA1/J mice by enhancing IgG glycosylation leading to reduction in inflammation. It also hindered the NF-κB pathway and NFATc1/c-Fos which diminished the activity of osteoclasts [63]. All these beneficial outcomes of Gen delivering medicinal properties conclude this phytoestrogen as a potential compound to be used for RA phytotherapy.

9. Daidzein

Daidzein is a plant derived phytoestrogen with molecular formula $C_{15}H_{10}O_4$ and MW254.24 g/mol. Daidzein is one of the main phytoestrogens found in soybeans and falls under the category of isoflavones [64]. It exhibit antioxidant, anti-neoplastic and phytoestrogenic properties [65]. This phytoestrogen is the most accepted compound to be utilized for RA conditions.

The protective effect of Daidzein on RA was reported in 2011 by Mohammad-Shahi et al. where a attenuation in disease symptoms and also delay in onset of symptoms were observed in RA induced female Sprague-Dawley rats using col II plus adjuvant after Daidzein treatment. The ear thickness in treated rats was found to be less than control rats [59]. In another study CIA induced female Sprague-Dawley rats were used again for observing other defensive properties of

Daidzein against RA. In this study it was shown that after treating the rats with 20 mg/kg Daidzein for 50 days daily there was a restoration of paraoxonase and arylesterase activity and MDA concentrations were also decreased after the treatment [60] which helps in reducing the risk of artherosclerosis in RA patients [61]. In 2016, Ahmad et al. showed that upon administration of Daidzein in CIA Wistar albino rats intradermally in the tail region and also orally (50 mg/kg body weight) for 21 days, a significant decrease in articular elastase activity, TNF-α and MDA levels were observed. The plasma lowdensity lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglyceride were also suppressed along with reduction in arthritic score. Anti-oxidant property was also reported after demonstrating total antioxidant level elevation in plasma of arthritic animals followed by decrease in free radical load [66]. Daidzein plays an important role in reducing osteoclast formation as it was demonstrated that Daidzein (10^{-5} M) significantly hindered TRAP positive osteoclast formation and resorption area and inhibited the action of estrogen inhibitor ICI 182,780 in causing pro-osteoclastic effect. It also reduced TNF-α-induced *c-fos* and *NFATc1* expression in an ER dependent manner along with inhibiting NFATc1 nuclear translocation and decreasing *NFκB* and *DC-STAMP* levels in RAW 264.7 cells [62]. A recent study by Du et al. in 2020 reported Diadzein to attenuate joint damage in Diadzein (20 mg/kg) treated female DBA1/J mice with CIA by increasing IgG glycosylation and inhibiting osteoclast activity. The expression of B4galt1 (galactosylation) and St6gal1 (sialylation) genes were found to be higher in Diadzein treated groups compared to the CIA group and inhibition of NF-κB pathway and NFATc1/c-Fos was observed which reduced the activity of osteoclasts [63]. Manifestation of these therapeutic abilities of Daidzein deduces it to be a highly potential compound for targeting RA.

10. Hesperidin

Hesperidin (HES), a disaccharide derivative commonly found in citrus fruits with molecular formula $C_{28}H_{34}O_{15}$and MW is 610.6 g/mol. This vitamin P bioflavonoid is used as a medicine as it helps blood vessels to function better and reduce inflammation. Anti-inflammatory property and protective effects of HES were reported in the study by Fu et al., 2018 where a marked decrease in production of NO, Pg E2, NOS and cyclooxygenase-2 were observed in HES treated IL-1β-stimulated chondrocytes. Furthermore, downregulation of IL-1β-induced MMP-3 and MMP-13 expression was reported along with suppression of activation of NF-kB signalling pathway [67]. Several experiments were conducted to analyse the potential of HES in preventing RA progression.

In 2016, Ahmad et al. showed that upon administration of HES in CI Wistar albino rats intradermally in the tail region and also orally at a concentration of 50 mg/kg body weight for 21 days, a significant reduction in articular elastase activity, TNF-a, and MDA levels were observed. The plasma lowdensity lipoprotein cholesterol, very low- density lipoprotein cholesterol, and triglyceride were also suppressed along with reduction in arthritic score. Elevation in total antioxidant level and reduction in free radical load in plasma of arthritic animals demonstrated its antioxidant property. Similarly *in vitro* studies demonstrated enhancement of free radical scavenging activity of HES against 2,2-diphenyl-1-picrylhydrazyl and 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid in addition to anti-inflammatory, hypolipidemic, and antioxidant actions [66]. Another *in vivo* study on complete FCA-induced rats, protective nature of HES against RA was displayed by analysing specific rheumatoid biomarkers like Serum rheumatoid factor, MMP-3 and cartilage oligomeric matrix protein (COMP), immunological biomarkers like serum IgG, antinuclear antibody (ANA), immunomodulatory cytokines like serum TNFα and IL-10, inflammatory biomarkers like serum myeloperoxidase (MPO) and C-reactive protein and oxidative stress biomarkers like MDA and glutathione (GSH) which got restored to normal level after administration of HES (200 mg/kg/day) in RA induced rats [68]. Similar kind of study by Guardia et al., 2001 showed the anti-inflammatory activity of HES in rat model with adjuvant-carrageenan-induced inflammation (ACII) where inhibition of both acute and chronic phases of this experimental model was observed [69]. In CIA mouse model of RA, administration of Citrus flavonoid HES showed significant reduction in clinical scores and improvement in histological features [70]. Another study by Qi et al., it was shown that HES induction in FLS cells and macrophage M1 and M2 polarization markers induced by LPS caused a decrease in expression level of MMP3, MMP9, MMP13 and degree of polarization of macrophages to M1. They also reported an inhibition of the PI3K/AKT signalling pathway in complete FCA induced arthritic mice by HES (20 mg/kg/day) treatment [71]. Moreover restoration in articular elastase, NO, lipid peroxidation, GSH, superoxide dismutase activity and catalase were observed in HES treated CIA rats in comparison with control group [72]. These reports on inhibition of disease related inflammatory factors and marker proteins by HES concluded the efficacy of this phytoestrogen in treating RA conditions.

11. Kaempferol

Kaempferol, chemically known as 3,4′,5,7-tetrahydroxyflavone, with molecular formula $C_{15}H_{10}O_6$ and MW 286.23 g/mol belongs to the class of flavonoids. It is commonly present in herbs, fruits and vegetables including beans, cabbage, grapes, tomatoes, broccoli, tea, kale, endive, leek and ginkgo biloba leaves. It is commonly used in traditional medicine and is known for exhibiting pharmacological properties like antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, and anticancer activities [73,74]. RA condition is known to get inhibited by Kaempferol treatment in several *in vitro* and animal experiments. Therapeutic activities of Kaempferol against RA were demonstrated in miscellaneous experiments in recent years.

In a study by Lee et al. in 2018 it was suggested that Kaempferol can act as a therapeutic agent for RA as *in silico* molecular docking study as well as *in vitro* and *in vivo* studies proved Kaemferol as an inhibitor of bFGF-FGF receptor 3 (FGFR3) kinase domain. This resulted in suppression of (FGFR3)-ribosomal S6 kinase 2 (RSK2) signalling axis which consequently inhibited the proliferation and migration of RA-FLSs, osteoclast differentiation, reduced osteoclast markers, such as tartrate- resistant acid phosphatase, integrin β3, and MMP9 followed by suppressing the secretion of activated T-cell-mediated inflammatory cytokines like IL-17, IL-21, and TNF-α [75]. Kaempferol was found to reduce migration, invasion and MMP expression in RA-FLSs and also attenuated actin cytoskeleton reorganization during cell migration along with suppression of TNF-α-induced MAPK pathway activation without affecting the expression of TNF-α receptors leading to decrease in severity of arthritis in CIA mice [76]. Another instance of Kaempferol protective nature against RA was reported in a study by Yoon et al. in 2013 where he showed the inhibition of proliferation of both unstimulated and IL-1βstimulated RA synovial fluids (RASFs), as well as the mRNA and protein expression of MMP-1, MMP-3, COX-2 and PGE2 induced by IL-1β. It also hindered phosphorylation of ERK1/2,

p38 and c-Jun N terminal kinase (JNK) and inhibited NF-kB after the treatment with Kaempferol [77]. Kaempferol was reported to prevent bone loss by inhibiting osteoclast formation as it decreased expressions of c-Fos and NFATc1 along with inhibiting IL-1β-stimulated RANKL-mediated osteoclast differentiation and RANKL-mediated phosphorylation of ERK 1/2, p38 and JNK MAP kinases [78]. *In vitro* study in IL1β induced SW982 cell line after treatment with Kaempferol at concentrations of 2, 10 and 50 μmol/L significantly reduced IL-6, IL-8, MMP-1, and COX-2 mRNA and protein level expressions along with suppression of MAPK and protein kinase B (Akt) phosphorylation and diminished IκB-α degradation and p65 protein translocation into the nucleus [79]. These anti-arthritic properties of Kaempferol ratified this phytoestrogen to be a suitable compound for RA therapy.

12. Leonurine hydrochloride

Leonurine hydrochloride (LH) is a major alkaloid compound with molecular formula $C_{14}H_{21}O_5N_3$.HCl and MW 311.33 g/mol derived from leonurine. It is extracted from motherwort (Leonurus cardiac)and is known for exerting phytoestrogenic activity [80]. It is known to exhibit anti-oxidative, anti-inflammatory, anti-tumor and anti-diabetic activities along with cardiovascular and bovine mastitis protection [81]. Several experiments were performed for detecting the ability of this alkaloid in protecting RA.

LH is proved to be a potent therapeutic compound as in the study by Yuan et al. 2015 it has been shown that LH repressed RANKL-induced osteoclastogenesis and actin ring formation by inhibiting NF-κB signalling which caused retardation of phosphorylation and degradation of IκBα and NF-κB p65 nuclear translocation. RANK-TRAF6 association which is activated by RANKL binding and PI3-K/Akt axis was also inhibited by LH treatment, without significantly affecting the extracellular signal-regulated kinase (ERK)/MAPK and AP-1 signalling pathways in RAW 264.7 cells and mouse bone marrow monocytes (BMMs). Moreover LH treatment suppressed expression of RANKL-stimulated osteoclast-linked genes including NFATc1, tartrate resistant acid phosphatase (TRAP), cathepsin K and osteoclast-associated receptor. Not only in *in vitro* study, attenuation of osteoclast activity was also reported in *in vivo* study in mice leading to prevention of bone loss occurred by estrogen deficiency [82]. LH treatment in RA fibroblast-like synoviocytes resulted in decrease of pro-inflammatory cytokines such as IL-1β, Il-6, IL-8 and TNF-α and MMPs like MMP-1 and MMP-3 production and attenuated TNF-α-induced NF-kB signalling which prevented nuclear translocation of the NF-kB p65 subunit along with suppression of migration and invasion of RA-FLS. Moreover in CIA model it significantly reduced p38 and JNK MAPK signalling pathways and serum IL-1β, IL-6 and TNF-α levels leading to suppression of synovial inflammation and joint damage [83]. These reports suggested that this phytoestrogen can be utilized for treating RA conditions after positive clinical trials.

13. Luteolin

Luteolin (Lut), chemically known as 3′,4′,5,7-tetrahydroxy flavones with molecular formula $C_{15}H_{10}O_6$ and MW 286.24 g/mol. It is a naturally occurring flavonoid biophenol mostly found in different fruits and vegetables like carrots, peppers, celery, olive oil, peppermint, thyme, rosemary, and oregano and also present in flowering plants [84]. It is known for exhibiting various pharmacological properties such as antioxidant, anticancer, anti-inflammatory, and neuroprotective effects [85, 86]. This yellow compound is known to be effective against RA conditions supported by some specific *in vitro* and *in vivo* experiments.

Lut is effective against RA and it was demonstrated in SW982 cells, where after treatment with Lut at 1 or 10 μl there was a significant inhibition of IL-1b-induced MMPs that is MMP-1 and MMP-3 and cytokines like TNF-a and IL-6 production along with suppression of MAPKs including JNK and p38 and transcription factors AP-1 and NF-kB [87]. *In vivo* study in FCA-induced arthritic rats also revealed the anti-arthritic activity of Lut as there was a reduction in severity of arthritic scores as well as TNF-a, IL-6, IL-1b and IL-17 expression levels after Lut administration. Moreover a significant inhibition of P2 × 4, NLRP1, ASC, and Caspase-1p10 has been observed in treated rats compared to control group [88]. Luteolin inhibited proliferation of synovial fibroblasts in CIA rats causing a delay of cells in the G_2/M phase along with decreasing the secretion of MMP-1, MMP-3, IL-6, IL-8, IL-15, and TGF-β and inhibited the MAPK/ERKs and PI3K-Akt pathways [89]. Data related to anti-arthritic, anti-inflammatory and other pharmacological activities of Lut targeting RA suggest this compound as an effective phytomedicine.

14. Medicarpin

Medicarpin (Med), is a pterocarpan-type phytoalexin, benzopyran furanobenzene compound with molecular formula $C_{16}H_{14}O_4$ and MW 270.28 g/mol [90]. It belongs to the group of flavonoids and mostly found in chickpea (*Cicer arietinum*), peanut (*Arachis hypogaea*), alfalfa (*Medicago sativa*), red clover (*Trifolium pratense*) and in an Indian medicinal plant *Butea monosperma* and *licorice* [91]. Med exhibits anti-proliferative activity and is effective against cancers like breast cancer and acute myeloid leukaemia and also inhibits ER stress-induced apoptosis [90]. Anti-arthritic property of Med is well known and it has been simultaneously examined in case of RA.

In 2020, Mansoori et al. had shown the antiarthritic property of Med in CIA ovx mice where prevention of TH-17/Treg ratio alteration, reduction in osteoclastogenesis and pro-inflammatory cytokines like TNF-α, IL-6 and IL-17A expression levels and upregulation of IL10 were observed. Moreover Med treatment in mice prevented cartilage erosion in joints and restored loss of trabeculae parameters in distal tibia along with restoration of COMP which is a biological marker of arthritis [92]. In a study by Tyagi et al. in 2010 it has been shown that induction of Med at a concentration of 10^{-10} M decreased osteoclastogenesis in bone marrow cells (BMCs) and caused apoptosis of mature osteoclasts. Similarly in ovx mice administration of med at a dose of 10.0 mg kg^{-1} day^{-1} orally for 30 days decreased formation of osteoclasts but elevated the formation of osteoprogenitor cells in BMCs along with maintaining the parameters of trabecular microarchitecure [93]. Another study by Tyagi et al. in 2011, reported that Med induction in ovx mice caused thymus involution and decreased ovx-induced increase in serum TNF-α mRNA and protein levels in the BM T cells along with

reduction in proliferation of BM and spleen $CD4^+$ T cell and averted CD28 loss on $CD4^+$ T cells and in the BM T cells [94]. These osteoclast prevention reports of Med propose this flavone to be utilized in RA conditions.

15. Coumestrol

Coumestrol with molecular formula $C_{15}H_8O_5$ and MW 268.22 g/mol is included in the group of coumestan isoflavones. It is produced mainly in plants like soybeans, clover, alfalfa, sprouts, sunflower seeds, spinach, and legumes [95]. Having similar structure and function as that of 17-estradiol, it easily binds to human estrogen receptor (hER) and is known for exhibiting anti-inflammatory agent, antioxidant and antimicrobial property [96]. This natural organic compound reduces risk of various diseases including RA.

The protective nature of coumestrol was demonstrated in a study in 2017 where it eradicated IL-1β-induced loss of proteoglycans and knee articular cartilage and decreased NOS, cyclooxygenase-2, Pg E2 and the expression of matrix-degrading enzymes such as MMP-13, MMP-3 and MMP-1 and inflammatory cytokines in primary rat chondrocytes stimulated with IL-1β [97].Role of coumestrol in postmenopausal bone loss was reported by Draper et al. where coumestrol treatment in oophorectomized (OOX) rat model showed significant reduction in bone loss, urine calcium excretion and in expression of bone resorption markers pyridinoline and deoxypyridinoline after 1 week of treatment [98]. Coumestrol plays an important role in reducing osteoclast formation as it was demonstrated that coumestrol significantly reduced TRAP positive osteoclast formation and resorption area and inhibited the action of estrogen inhibitor ICI 182,780 in causing pro-osteoclastic effect. It also reduced TNF-α-induced *c-fos* and *NFATc1* expression along with inhibiting NFATc1 nuclear translocation and*NFκB*, *DC-STAMP* levels in RAW 264.7 cells [62]. Coumestrol at a concentration of 10^{-7} M was also found to suppress the formation of con A activated T cells induced TRAP positive osteoclast, which was dependent on attenuation of T cell derived TNF-α. It also decreased T cell number and TNF-α, IL-1β and IL-6 expression levels [99]. Both *in vitro* and *in vivo* studies provide a definite proof of this phytoestrogen to be beneficial for RA treatment.

16. Puerarin

Puerarin also known as Kakonein, is a hydroxyisoflavone with molecular formula $C_{21}H_{20}O_9$ and MW 416.4 g/mol. This compound is found in a number of plants and herbs, such as the root of the kudzu plant. It shows antioxidant property and protect against cell damage caused by lipid peroxidation [100]. Having all these pharmacological properties, this bioactive ingredient was also analysed in different experimental systems for detecting its effectiveness against RA.

In vivo study in CIA induced arthritic mice after puerarin treated resulted in significant decrease in arthritic scoring of CIA and suppressed oxidative stress and inflammatory response in mice along with inhibition of NF-κB activity, phosphorylated (p)-Janus kinase 2 and p-signal transducer and activator of transcription 3 protein expressions [101]. In a study by Xiao et al., 2011, tetraacetylpuerarin (4AC) which was prepared from puerarin through acetylation for better liposolubility and bioavailability had been administered to LPS-induced RAW264.7 macrophages and bovine type II CIA rats and a significant increase in the activity of superoxide dismutase (SOD) and reduction in the level of MDA and TNF alpha were observed. NF-κB expression and down-regulation of the levels of p-ERK and p-JNK was demonstrated in *in vitro* studies whereas improvement in the level of glutathione peroxidase (GSH-PX) and the total antioxidant capacity was observed in *in vivo* study [102]. *In vitro* study proved puerarin as a promising candidate drug for the prevention and treatment of bone destruction disease as in this study it was shown that puerarin treatment on RAW264.7 cells inhibited LPS-induced Akt expression and osteoclast differentiation by suppressing the production of osteoclast activating factor TNF-α, IL-1β and PGE2, leading to down-regulation of mRNA expression of osteoclastogenic genes including TRAP, cathepsin K and MMP-9. *In vivo* experiments on murine calvarial osteolysis model also supports similar kind of results [103].Clinical studies on 119 patients with a definite diagnose of active RA treated with and without puerarin (400 mg) resulted in significant decrease of carotid intima-media thickness (CIMT) and improvement in insulin resistance after 24 weeks of treatment [104]. With support of clinical studies, various experiments gave a definite indication for utilizing this compound in phytotherapy against RA

17. Pterostilbene

Pterostilbene with molecular formula $C_{16}H_{16}O_3$ and MW 256.296 g/ mol is included in the class of phytoalexin and is generally found in blueberries and grapes [105].

In vitro study in E11 human rheumatoid arthritis synovial fibroblasts proved anti-inflammatory properties of pterostilbene as its treatment suppressed LPS induced NF-κB p65 nuclear translocation, reduced the secretions of IL-6, IL-18, VEGF, nitric oxide, MMP-2 and MMP-9 in E11 cells and hindered E11-driven migration of THP-1 and U937 monocytes along with suppressing LPS-induced pro-inflammatory cytokines in THP-1 cells [106]. Antioxidant property of pterostibene in protecting arthritis was shown in the study by Perecko et al.2013 where significant reduction in number of neutrophils in blood on day 14 and 21 of administration of pterostilbene (30 mg/kg, daily) was reported without significant depletion of neutrophil oxidative burst in experimental model of arthritis. It also significantly improved total radical trapping potential in the arthritic animals [107]. *In vivo* study on Adjuvant induced arthritis (AA) induced rats demonstrated that pterostilbene administration orally at a dose of 30 mg/kg body weight daily resulted in partial effect on luminol-enhanced CL of the joint [108]. These anti-inflammatory and antioxidant activities suggested this phytoestrogen to be a potential compound in RA phytotherapy.

18. Reserveratrol

Resveratrol (RSV) with molecular formula $C_{14}H_{12}O_3$ and MW 228.25 g/mol falls in the category of polyphenols' stilbenoids group. It is commonly found in grapes skin, seeds, red wines and various human foods and also synthesized from yeasts Saccharomyces cerevisiae. This phytoalexin possesses antimicrobial, antioxidant, antitumor, inflammatory, anticarcinogenic, cardioprotective, vasorelaxant, phytoestrogenic and neuroprotective properties [109]. Possessing all these pharmacological parameters, researchers evaluated this compound in various experiments to assess its clinical activities against RA.

In arthritic rat model, effect of RSV was analysed and an increase in IL-4 concentration and decrease in RF serum levels and ACPAs gingival levels was observed. Phenotypically smooth articular surface and increase in width of the subchondral cortical along with reduction in articular damage were observed after RSV treatment [110]. Combined effect of

RSV (50 mg/kg) and Piperine (PIP) (50 mg/kg) in AA in rats decreased the paw swelling and ameliorated the histopathological changes as well as serum TNF-a, IL-1b, thiobarbituric acid reactive substances (TBARS), NF-kB p65 and NO expression level were reduced [111].Another study by El-Ghazaly in 2020 reported a reduction in the paw swelling and a significant attenuation in the serum levels of TNF-α, IL-1β, TBARs, and NO along with suppression of NF-κB p65 expression after administration of RSV orally in FCA induced rats exposed to low dose radiation at a total exposure level of 0.5 Gy (2 × 0.25) [112]. Clinical studies also proved the therapeutic effects of RSV in RA as the treatment of RSV as capsule of 1 g to RA patients for 3 months lowered the clinical markers like the 28-joint count for swelling and tenderness and the disease activity score for 28 joints and there was a significant decrease in serum levels of certain biochemical markers i.e., C-reactive protein, erythrocyte sedimentation rate, undercarboxylated osteocalcin, MMP-3, TNF-α, and IL-6 [113]. Combination of these *in vitro*, *in vivo* as well as clinical studies conferred this phytoestrogen as an ideal compound to be used for RA therapy.

19. Pinosylvin

Pinosylvin (Pin) with molecular formula $C_{14}H_{12}O_2$ and MW212.244 g/mol, is a natural stilbenoid found in pine leaf (*Pinus densiflora*) and the heartwood of Pinus spp. (*Pinus sylvestris*). It is commonly used in traditional medicines and is known to exhibit anti- microbial properties [114]. The activity of this well-known compound was analysed in various studies including *in vitro* as well as animal models of RA conditions.

It has been shown to exhibit antioxidant properties by reducing oxidative stress and also altered immunological parameters effectively in AA model in Lewis rats proving its suitability as monotherapy for RA or in combination with methotrexate [115]. Another *in vivo* study in AA rats after Pin monotherapy or in combination with methotrexate (MTX) was conducted by Bauerova et al., 2015 which reported significant reduction in oxidative stress by increase of heme oxygenase 1 (HO-1) expression, decrease of plasmatic TBARS and reduction of lipooxygenase (LOX) activity in the lung [116]. *In vitro* study in fresh human blood neutrophils, Pin at 10 μmol/L and 100 μmol/L significantly diminished the formation of oxidants, both extra and intracellularly, and effectively attenuated protein kinase C (PKC) activation stimulated by phorbolmyristate acetate (0.05 μmol/L). Moreover in the *in vivo* experiment of Pin treatment in AA in Lewis rats, the number of neutrophils in blood which got increased during arthritis induction decreased significantly along with significant reduction in the amount of reactive oxygen species in blood [117]. Another *in vivo* study on AA rats demonstrated that Pin administration orally at a dose of 30 mg/kg body weight daily resulted in diminishing human papilloma virus (HPV), CL of the joint and MPO activity of the joint homogenate when compared to untreated animals which proved Pin as an effective compound to be utilised for exerting anti-inflammatory and antioxidant effect reducing oxidative stress induced biochemical changes occurring in AA [108]. Apart from antimicrobial properties these reports suggested an active role of this phytoestrogen in protecting RA.

20. Silibinin

Silibinin with molecular formula $C_{25}H_{22}O_{10}$ and MW482.44 g/mol is a flavonoid, extracted from the medicinal plant *Silybum marianum* (milk thistle) and is the major active constituent of silymarin [118]. It is known to exhibit anti-neoplastic effects including skin, breast, lung, colon, bladder, prostate and kidney carcinomas and hepatoprotective (anti-hepatotoxic) properties [119].

In a study by Tong et al. 2018, it has been shown that silibinin treatment in RA pathogenesis-related cells and CIA model resulted in inhibition of the production of inflammatory cytokines as well as suppression of NF-κB pathway and decrease of Th17 cell differentiation. In RAW264.7 cells, induction in macrophage M2 polarization was observed. Moreover silibinin decreased cell viability, autophagy and increased the percentage of apoptotic RA-FLS along with the inhibition of Sirtuin1 (SIRT1) in RA-FLS [120]. Silibinin protective nature against RA was demonstrated in 2018 in a study by Dupuis et al. where silibinin was found to modulate ERβ expression in T lymphocytes, increased ERβ expression, induced apoptosis, attenuated proliferation, and decreased expression of the pro-inflammatory cytokines IL-17 and TNF-α, through ERβ binding in T lymphocytes. Silibinin also acted as an epigenetic modifier, down regulating the expression of miR-155 which is known for strongly contributing RA pathogenesis and activating the immune system [121]. Silibinin also improved the effect of methotrexate in active RA cases as significant decrease in the already elevated clinical scores, ESR, IL-8, IL-6, TNF-α, anti-CCP, high sensitivity C-reactive proteins (hs-CRP) levels were observed compared to placebo treatment along with a significant increase in haemoglobin (Hb), IL-10, and IL-2 levels [122]. This was also proved in an *in vivo* study where silibinin was found to increase the effectivity of methotrexate in zymosan-induced arthritis animal model [123]. Silibinin was reported to inhibit osteoclast formation as it attenuated receptor activator of RANKL-induced osteoclastogenesis both in RAW264.7 cells and BM-derived monocyte/macrophage cells by obstructing the activation of NF-κB, c-JNK, p38 MAPK, and ERK and suppressing the induction of NFATc1 and osteoclast-associated receptor (OSCAR) expression during RANKL-induced as well as TNF-α-induced osteoclastogenesis [124]. These immunosuppressive activities of silibinin signify this phytoestrogen as an effective compound against RA progression.

21. Quercetin

Quercetin is a natural plant pigment with molecular formula$C_{15}H_{10}O_7$ and MW302.236 g/mol and is included in the group of flavonoids. It is present in various fruits, vegetables and grains, mostly found in red wine, onions, green tea, apples, berries, Ginkgo biloba, St. John's wort, American elder, Buckwheat tea. It is used as a medicine as it imparts antioxidant activities by combating free radical damage and reduce inflammation and allergy symptoms as well as it is used to treat conditions of the heart and blood vessels, arthritis, bladder infections, and diabetes and also prevents cancer [125,126]. As this compound is found to be effective against various chronic diseases, this phytoestrogen was also thoroughly analysed in RA conditions for investigating its protective activities against this disease.

Quercetin is found to suppress inflammation in RA induced mice by inhibiting neutrophil activities and it also inhibited neutrophil extracellular trap (NET) formation by suppressing autophagy [127]. Quercetin treatment in RA-FLS leaded to apoptosis and decrease of RA-FLS viability by upregulating long non coding RNA (lncRNA) metastasis associated lung adenocarcinoma transcript 1 (MALAT1) which cause the apoptosis by activation of the PI3K/AKT pathway [128]. *In vivo* study on CIA C57BL/6 mice model after quercetin administration resulted in severe reduction in joint inflammation and expression levels of TNF-α, IL-1β, IL-17, and

MCP-1 [129]. Another *in vivo* study on adjuvant induced arthritis in rats after quercetin administration daily at 150 mg/kg body weight for 28 days decreased expression of IL-1β, C-reactive protein, and monocyte chemotactic protein-1, NF-κB activity and improved plasma antioxidant capacity along with inhibition of the enzymatic activity of pro-inflammatory 12/15-lipoxygenase in lung and liver and elevated the expression of HO-1 in joint and lung of arthritic rats [130]. Clinical trials had proved quercetin as a protective agent for RA as its supplementation for 8 weeks significantly diminished EMS, morning pain, after-activity pain, Plasma hs-TNFα level, DAS-28 and HAQ scores. Significant improvements in clinical symptoms, disease activity, hs-TNFα, and HAQ were also observed in women with RA after quercetin treatment [131]. Another clinical study on patients treated with different doses of quercetin demonstrated that quercetin at doses of 1500 mg/day, when added to 100 mg azathioprine, significantly

Table 2
In vitro studies of phytoestrogens with their mechanism.

Phytoestrogen	Cells/ Cell line	Mechanism	References
		↑caspase-3 and caspase-7	[24]
		MAPK ERK1/2	[24]
		↓Bcl-2/Bax	[26]
Apigenin	RA-FLSs	Inactivate PI3-K/Akt	[26]
		Restore p21 and p27	[26]
	BMDCs	↓MHC II, CXCR4	[28]
	Bone marrow	↓RANKL, Erk1/2	[33]
	macrophages	↓NFATc1, c-Fos, TRAF6, c-Src, Cathepsin K, Syk, PLCϒ2, Gab2	[33]
		↓Bcl-2, ↑Bax	[34]
Arctigenin	RA FLS	Activating mitochondrial pathway, ↓caspase-9, caspase-3, PARP, p65, degradation of IKBa	[34]
	Raw264.7	↓TNFα, MKK, MAP Kinase, ERK1/2, P38 kinase, AP-1	[36]
Biochanin A	RAW264.7 macrophages	↓TNFα, IL-6	[40]
		↓RANKL	[42]
Bavachin	RAW264.7	↓Tartarate-resistant acid phosphatase, matrix metalloproteinase-9, cathepsin K, nitric oxide synthase, cyclooxygenase-2, prostaglandin E2	[42]
	THP-1 monocytic cells	↓IL-1β induced NFkB, IkBα kinase	[43]
		↑p65, p50	[43]
	Mesenchymal stem	↑ALP, OCN, OPN, Col-1	[50]
Formononetin	cell B cells	↓Th17, B cells, IL-17A	[51]
		↑FOXP3, Ovx-induced deterioration	[51]
	MH7A cells	↓IL-6, VEGF, STAT3	[54]
	EA.hy926 cells	↓IL-6	[54]
Genistein	TNFα induced MH7A	↓IL-1β, IL-6, IL-8, TNFα induced NFkB and AMPK, IkB kinase-α/β, IkBα, ROS/Akt/NFkB pathway	[55]
	RA FLS	IL-1β, TNFα, EGF, MMP9, Erk1/2	[58]
	RAW264.7	↓ICI, TNFα induced c-fos and NFATc1, NFkB and DC-STAMP	[62]
Daidzein	RAW 264.7	↓ICI 182,780, c-fos, NFATc1, NFkB, DC-STAMP	[62]
	IL-1β stimulated chondrocytes	↓nitric oxide, prostaglandin E2, nitric oxide synthase, cyclooxygenase2, IL1β induced MMP3 and MMP13,	[67]
Hesperidin		NFkB signalling	
	FLS	↓MMP3, MMP9, MMP13	[71]
	RA FLS	↓FGFR3 kinase, FGFR3-RSK2 signaling, tartarate resistant acid phosphatase, integrin	[75]
	RASFs	β3, MMP9 IL17, IL21, TNFα	[75]
Kaempferol		↓MMP1, MMP3, COX2, PGE2, ERK1/2, p38, JNK, NFkB	[77]
	Osteoclast	↓c-Fos, NFATc1, IL1β, RANKL, ERK1/2, p38, JNK, MAP kinase	[78]
	IL1β induced SW982	↓IL6, IL8, MMP1, COX2 mRNA, MAPK, Akt, IkBα, p65	[79]
Leonurine hydrochloride	RAW 264.7	↓NFkB p65 signaling, IkBα, RANKL, PI3K/Akt, ERK/MAPK, AP-1	[82]
	RA FLS	signaling ↓IL-1β, IL-6, IL-8, TNFα, MMP1, MMP3, NFkB p65	[83]
Luteolin	SW982	↓MMP1, MMP3, IL-6, TNFα, MAPKs (JNK and p38), NFkB, AP1	[87]
Medicarpin	BMCs	apoptosis	[93]
Coumestrol	RAW 264.7	↓TRAP, TNFα induced c-fos and NFATc1, NFkB, DC-STAMP	[62]
	Osteoclast	↓TNFα, IL1β, IL6	[99]
	RAW 264.7 macrophages	↑SOD	[102]
Puerarin		↓pERK, p-JNK	[102]
	RAW 264.7	↓TNFα, IL1β, PGE2, TRAP, cathepsin K, MMP9	[103]
Pterostilbene	E11 human synovial fibroblasts	↓NFkB p65, IL6, IL18, VEGF, nitric oxide, MMP2, MMP9, THP1	[106]
	Neutrophils	↑total trapping potential	[107]
Resveratrol	RSV	↓C-reactive protein, MMP3, TNFα, IL6	[113]
Pinosylvin	neutrophil	↓PKC activation	[117]
	RAW 264.7	↓NFkB, Th17 cell differentiation, SIRT1, RA FLS	[120]
Silibinin	RAW 264.7 and monocyte	↑RANKL, TNFα	[124]
		↓NFkB, c-JNK, p38 MAP, ERK, NFAT, OSCAR	[124]
Quercetin	RA FLS	↑lncRNA MALATI, PI3K/AKT	[128]
Ginsenoside	RAW264.7	↑PPARϒ	[138]
		↓IkBα phosphorylation, NFkB, TNFα, IL6	[138]

reduced IL-6, complement protein 3 (C3), complement protein 4 (C4), intercellular adhesion molecule-1levels and elevated IL-10 level compared to control groups [132]. These well studied experiments along with clinical trials on quercetin treatment conclude this compound as an effective one for treating RA.

22. Ginsenoside

Ginsenosides also known as panaxosides are included in the class of steroid glycosides. It is found commonly in plant genus Panax (ginseng) [133]. Ginsenosides exhibit medicinal properties such as antitumor, anti-inflammatory, antioxidation, and inhibition of cell apoptosis [134]. Ginsenosides Rg1 (G-Rg1) and Rb1 (G-Rb1) demonstrates estrogen-like activity and could inhibit hepatitis A virus titres and exhibit certain immunomodulatory properties [135,136]. G-Rg1 and G-Rb1 are examined under different RA *in vitro* and *in vivo* conditions to analyse its therapeutic potential.

G-Rb1 was reported to display anti-arthritic effects as it was found to significantly suppress TNF-α upregulation in peripheral blood mononuclear cell (PBMCs), FLS and chondrocytes induced by IFN-γ, LPS or IL- 1. It also ameliorated the clinical arthritis score, reduced cell infiltration and cartilage destruction in the arthritic joint and decreased TNF-α expression in the CIA mice [137]. G-Rg1 has been demonstrated to exhibit anti-arthritic effects as G-Rg1 induction at doses of 5, 10, and 20 mg/kg intraperitoneally for 14 days on AA in rats showed significant

Table 3
In vivo studies of phytoestrogens with their mechanism.

Phytoestrogen	Animal model	Mechanism	References
Apigenin	Arthritic rats	↓P2 × 7/NF-kB, TNFα, IL-1β, IL-6	[27]
		↓MHC II, CXCR4	[28]
	CIA rats	↓Proliferation in FLS	[28]
		↓VEGF, VEGFR	[28]
	CIA mice	RANKL/RANK/OPG	[29]
Arctigenin	Mice	↓osteoclast differentiation	[33]
		↓Ti particle, RANKL, p65	[35]
	In vivo osteolysis	Activation of NFkB	[35]
		Retardation in IkBα degradation	[35]
Biochanin A	Rat chondrocytes	↓MMP-13, MMP-3, MMP-1, ADAMTS-5	[39]
		↓Nitric oxide synthase 2, cyclooxygenase-2, prostaglandin E2,	[39]
	LPS stimulated mouse	inflammatory cytokines PPARϒ dependent pathway, GW9662 ↓TNFα, IL-6	[40]
			[40]
Equol	CIA mice	↓IL-6	[46]
	Osteoporotic mice	Fat accumulation	[47]
Formononetin	CIA mice	↓IkBα, NFkB p65	[48]
	Rat	↑VEGF, VEGF-2/flk-1	[50]
Genistein	CIA mice	↓DTH	[56]
		↓IFN, IL-4	[57]
		Balance between Th1/Th2	[57]
	Female Sprague-Dawley rat	↑collagen type II	[59]
		↓MDA	[60]
Daidzein	Female Sprague-Dawley rat	Collagen type II	[59]
	CIA female Sprague-Dawley rat	Restoration of paraoxonase and arylesterase	[60]
		↓MDA	[60]
	Wistar albino rats	↓TNFα, malondialdehyde	[66]
Hesperidin	Wistar albino rats	↓TNFα, malondialdehyde	[66]
	Freund's adjuvant induced rats	MMP3, COMP, IgG, ANA, IL10, MPO, MDA, GSH	[68]
	Rat	ACII	[69]
	CIA mouse	Suppression of clinical scores and improvement of histological features	[70]
	Freund's adjuvant induced arthritic mice	PI3K/AKT signaling	[71]
	Collagen induced arthritic rats	Restore nitric oxide, lipid peroxidation, glutathione, superoxide dismutase and catalase	[72]
Kaempferol	CIA induced mice	↓MAPK pathway	[76]
Leonurine hydrochloride	Mouse (BMMs)	↓NFkB p65 signaling, IkBα, RANKL, PI3K/Akt, ERK/MAPK, AP-1 signaling, NFATc1,	[82]
	CIA model	TRAP, cathepsin K, OSCAR	[83]
		↓p38, N terminal kinase, IL1β, IL-6, TNFα	
Luteolin	FCA-AA rats	↓TNFα, IL6, IL1b, IL17, P2 × 4, 36 NLRP1, ASC, Caspase 1p10	[88]
	Collagen induced arthritic rats	↓metalloprotease1,3, IL6, IL8, IL15, TGFβ, MAPK/ERKs, PI3K-Akt	[89]
Medicarpin	CIA mice	↓TNFα, IL6, IL17A	[92]
	Ovx mice	COMP restoration	[92]
		↓TNFα, BM T cells, CD4 + Tcell	[93]
		Formation of osteoprogenitor cells	[94]
Coumestrol	IL1β induced rat chondrocytes	↓matrix metalloproteinase 13,3,1, nitric oxide synthase, cyclooxygenase2,	[97] [98]
	OOX rat	prostaglandin E2 ↓pyridinoline and deoxypyridinoline	
Puerarin	CIA induced arthritic mice	↓NFkB pJK2, p signal tranducer	[101]
	CIA rats	↑SOD, GSH-PX	[102]
		↓MDA, TNFα	[102]
	Murine calvarialosteolysis model	↓TNFα, IL1β, PGE2, TRAP, cathepsin K, MMP9	[103]
Pterostilbene	AA induced rats	Partial effect on luminol enhanced CL	[108]

	Arthritic rat	↑IL4	[110]
	AIA rats	↓RF serum and ACCPA gingival	[110]
Resveratrol		↓TNFα, IL1β, TBARS, NFkB p65, NOx	[111]
	FCA induced rats	↓TNFα, IL1β, TBARS, NFkB p65, NOx	[112]
	Lewis rats	↓oxidative stress	[115]
	AA rats	↑NFkB, HO-1, LOX, MCP-1, F2 isoprostanes	[115]
	Adjuvant arthritis induced Lewis rat	↓reactive oxygen species	[117]
Pinosylvin	AA induced rats	↓HPV, CL, MPO	[108]
	Humans	↑ERβ expression, apoptosis	[121]
Silibinin		↓IL-17, TNFα, miR-155	[121]
	Zymosan induced arthritic animal	↓ESR, IL-8, IL-6, TNFα, antiCCP, hs-CRP ↑Hb, IL-10, IL-2	[123] [123]
	RA induced mice	↓NET formation	[127]
Quercetin	CIA C57BL/6 mice	↓TNFα, IL1β, IL-17, MCP1	[129]
	AA induced rats	↓IL1β, C reactive protein, monocyte chemotactic protein1, NFkB, 12/15 Lipoxygenase ↑heme oxygenase1	[130] [130]
	CIA mice	↓TNFα, FLS, chondrocytes	[137]
Ginsenoside	AIA rats	↑IFNϒ, LPS, IL1	[137]
		↓IkBα phosphorylation, NFkB, TNFα, IL6	[138]
		↑PPARϒ	[138]

reduction in joint swelling and injuries. IκBα phosphorylation and NF-κB nuclear translocation in the inflammatory joints reduced significantly along with decrease in level of TNF-α and IL-6 and increase in PPAR-γ protein expression in both AA rats and LPS stimulated RAW264.7 after G-Rg1 induction [138]. All these studies suggested that this phytoestrogen can be utilised in RA phytotherapy after proper clinical trials.

23. Conclusion

In light of the discoveries enumerated above, all these phytoestrogens more or less imparted therapeutic properties for protecting progression of this chronic disease RA. Possessing different medicinal implications including anti-inflammatory, anti-oxidant, anti- proliferative, anti-angiogenesis properties, these plant compounds showed the potential to be of substantial clinical benefit to RA patients. Phytoestrogen can be applied as cotherapy with currently used medicines like DMARDS, as long term use of synthetic medicines exerts adverse effects and patients disagree to continue these therapies. Phytoestrogen can replace the use of HRT and can be used as a bridge therapy before the onset of action of DMARDs. *In vitro* and *in vivo* studies demonstrating the protective nature of the phytoestrogens against RA are portrayed in Tables 2 and 3. During RA progression the immune homeostasis gets impaired where the immune components targets body's own cells leading to release of cytokines followed by chronic inflammation. Autoantibody production leading to emergence of Rheumatoid factor and anti-citrullinated proteins are the major triggers which activate complement system in joints and compel the T cells to infiltrate into the synovial membrane promoting the release of cytokines [139]. These pathophysiological mechanism of RA progression in the body is targeted by various phytoestrogens which directly or indirectly attenuate the release of inflammatory factors and cytokines such as IL-6, IL-1β, TNF-α (Fig. 2). Phytoestrogens targets various signalling pathways such as MAPK/ERK1/2 pathway, NFKB pathway and PI3K pathway which mediated the activation of disease progressing genes (Fig. 3). This cumulative action of phytoestrogen targeting different cells like TH17, osteoclasts, synovial fibroblasts, lymphocytes and hindering activation of inflammatory and disease progressing molecules proclaim these plant compounds as effective in protecting RA pathogenesis. Apart from attenuating chronic inflammation and specific joint damage, phytoestrogens are also effective in combating comorbid conditions in RA such as cardiovascular diseases, the most common cause of death in RA patients. Reports described above indicated the possibility to do further research and clinical trials of these phytoestrogens to develop better drugs based on these plant compounds for treating RA. Some of the phytoestrogens for instance Gen, Daidzein, HES, quercetin, RSV are found to have high therapeutic index and are well studied with quite a few clinical trials with RA patients suggesting their rapid transfer to clinical use. Combination of phytoestrogen with currently used synthetic drugs can also be a promising complementary therapy to treat RA patients.

To reduce the side effects of HRT or estrogen therapy, use of phytoestrogen has come to a trend which being structurally and functionally analogous to the estrogens compensates hormone deficiency in the body providing beneficial outcomes in various diseases including RA [140]. Not much is known about the adverse effects on consuming phytoestrogens, still some animal studies showed that it impacted fertility and morphogenesis of ovaries along with deregulating the hormonal developments [141,142]. So care should be taken on the usage and concentration of the phytoestrogens administered on patients to have minimal side effects. However various key questions are still unanswered: what is the role of these phytoestrogens in other arthritis? How much effective these would be when taken alone or in combination with commonly used drugs? Currently there are several ongoing clinical trials on the preventive effects of phytoestrogen on RA and more extensive researches are needed to establish a suitable phytotherapy for RA using proficient phytoestrogens.

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Declaration of Competing Interest

The authors report no declarations of interest.

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